Applicants respectfully traverse the restriction between all of the ten Groups. Applicants object to the Examiner's assertion that there are no special technical features linking the claims, and note that the Examiner supports the objection with the observation that HLA-G was known in the prior art, and further cites PCT Rules 13.1 and 13.2. Applicants do not agree with this interpretation of the application, as the invention is directed not towards HLA-G *per se*, but rather, broadly, to the diagnostic and therapeutic value of detecting particular polymorphisms in HLA-G in the field of some forms of abnormal pregnancies. The special technical feature of the invention, therefore, is not the HLA-G gene itself, but the use of the polymorphisms of the HLA-G gene in diagnosis.

Applicants point out that PCT Rule 13.2 defines the expression "special technical features" as 'those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.' In the case of the present invention, Applicants respectfully submit that it is evident to the person skilled in the art (that is, one practiced in the diagnosis of cited conditions afflicting pregnancy), that the feature that defines the contribution that the invention makes over the prior art is the method of diagnosis for the cited afflictions of pregnancy that are based on the polymorphisms of the HLA-G gene.

Applicants note that PCT Rule 13.2 states that the requirement of unity of invention shall be fulfilled where "there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features." In the case of the present application, the polymorphisms of the HLA-G gene used in the diagnosis of the cited conditions of pregnancy clearly involve the same special technical feature.

Applicants further submit that the cited prior art does not disclose or anticipate the present invention, nor does it disclose the special technical feature of the invention. Rather, the art cited by the Examiner merely discloses the HLA-G gene itself. Indeed, none of the cited art shows linkage between HLA-G and outcome of pregnancy, and therefore does not anticipate the special technical feature of the invention.

Applicants also wish to emphasize that the inventive concept of the present application is assessing the HLA-G allelic polymorphism of the individual in the diagnosis of pregnancy-associated problems.

There is a cause and effect chain of events that follow from a particular polymorphism in any gene. This will result in the DNA differing in sequence and possibly structure, and possibly its ability to bind proteins. This variant DNA may then give rise to a different type of mRNA expression; whether by increased or decreased levels of expression, a different size of mRNA species, or one of a different sequence, which in turn may be subjected to different levels or pressures of expression. The mRNA will in turn give rise to the proteins variants, which may also in turn be expressed or regulated or degraded at different levels, and interact differently with other cellular and extracellular components differently than other mRNA variants. It follows, therefore, that the cells of an individual with an allelic polymorphism will affect the DNA through mRNA to the expressed (or not) proteins and in the case of HLA-G will therefore affect the 'normal' level of HLA-G-peptide expression on the surface of the cell.

Indeed, the skilled artisan will appreciate that the same result (for example, detecting HLA-G polymorphisms for the purpose of diagnosing susceptibility to abnormal pregnancies) can be achieved utilizing several different approaches.

Applicants submit that to further restrict the subject matter for initial examination as proposed in the latest Restriction Requirement, e.g., to the use of a limited number of means of detecting the polymorphisms, would be unfairly restrict the scope of the invention. Applicants submit that the claims are closely interrelated and consideration and examination of all ten groups specified in the Restriction would not impose an undue burden.

For example, it is routine in the art to accurately predict a protein's size, level of expression, sequence, and to an extent, activity, by analyzing the mRNA. Similarly, it is also routine in the art to use the many various means of the invention to arrive at the same point, once the goal (diagnosis of susceptibility to abnormal pregnancies) and method (analysis of HLA-G polymorphisms) have been invented.

Applicants submit that the methods of all ten Groups are connected in design, operation, and effect, and that they all flow from a single inventive concept, that of the association between various HLA-G polymorphisms and a number of different pregnancy-related conditions. The instant claims are directed to various methods for directly and indirectly analyzing whether HLA-G polymorphisms may be present in a mother, father, and/or fetus. Based on this single inventive concept of assessing HLA-G polymorphisms associated with pregnancy-related conditions, Applicants feel that the instant restriction requirement unfairly limits Applicants' invention and respectfully request that all ten Groups be joined in the instant application.

In the event that the Examiner maintains the restriction requirement between Groups I-X, Applicants make the following arguments further traversing the restriction between certain specific Groups.

Applicants traverse the restriction between the inventions of **Groups I and IV**. Applicants traverse this group delineation on the basis that firstly, mRNA is a nucleic acid, and secondly, many of the methods used when determining the sequence of nucleic acid encompass those used in determining the size/level of nucleic acids. Therefore, Applicants respectfully submit that the inventions of **Groups I and IV** are directed to methods which are not "independent" and "distinct." Specifically, these methods are connected in design, operation, and effect, in that they are all directed to the analysis of nucleic acids, and that similar and/or identical experimental methods are often used to analyze both the sequence and the size/level of a nucleic acid. Applicants further traverse the restriction between **Groups I, IV, and VIII**.

Applicants submit that the methods of **Group VIII**, which encompass association, linkage, and/or transmission analysis, are intimately connected with the methods of **Groups I and IV**, in that association, linkage, and/or transmission analysis must necessarily be performed in conjunction with some type of nucleic acid analysis. Applicants still further traverse the restriction between **Groups I, IV, VII, and VIII**. Applicants submit that **Group VII**, which encompasses claims that are directed to quantifying molecules whose concentration changes as a result of HLA-G action, may include (but are not limited to) methods which measure changes in the concentration of HLA-G nucleic acids. Accordingly, Applicants request that these claims be examined in conjunction with the claims of **Groups I, IV, and VIII**.

Applicants also traverse the restriction between the inventions of **Groups II, III, and V**. Applicants respectfully submit that the inventions of **Groups II, III, and V** are directed to methods which are not "independent" and "distinct." Specifically, these methods are connected in design, operation, and effect, in that they are all directed to the analysis of polypeptides and that the same experimental methods are often used to analyze the size/level and the activity of a polypeptide, as well as variant forms of a polypeptide. Applicants further traverse the restriction between **Groups II, III, and V**, and **Groups VI, VII, VIII, IX, and X**. Applicants submit that the claims of **Groups VI, VII, VIII, IX, and X** are all directed to various methods for measuring, either directly or indirectly, the activity of the HLA-G protein, and are therefore not "indepedent and "distinct."

However, in the event that the restriction requirement is maintained in its entirety, Applicants hereby provisionally elect, with traverse, the invention of **Group I**, as this group reads on new claims **27-29, 33-36, 39-44, 62, 64 and 66-71**.

In addition to the restriction between Groups I-X, the Examiner has further required a species election of a specific HLA-G polymorphism where appropriate. With regard to this particular restriction, Applicants offer the following explanation of the nature of these HLA-G

polymorphisms which may be helpful. There are two polymorphisms at the heart of invention; the first of these is the C/T polymorphism of codon 93 in exon 3; and second of these is the insertion or deletion (i.e. presence or absence) of exon 8. An individual either has a C residue or a T residue at codon 93, and similarly will either have exon 8 (insertion) or not have exon 8 (deletion). The invention is directed to the elucidation of which specific polymorphisms are encoded by an individual's genotype. Therefore, the restriction requirement, specifically with respect to the third Group, appears to miss this distinction and thus, is improper. Specifically, the third Group does not accurately reflect the subject matter of original claim 2, which expressly recites both the insertion and deletion of exon 8 as the relative polymorphism.

Given that there are two different polymorphisms at the heart of the invention an individual will therefore fall into one of four possible genotypes, each of which indicates the different class of risk associated with pregnancy. The linkage between pre-eclampsia and HLA-G polymorphisms is intimately associated with the specific haplotypes donated by the mother and the father (*i.e.*, the single copy of the gene supplied by both the mother and the father to the fetus). Page 32, lines 24-25 of the application state "the maternally transmitted C-93/D-E8 haplotype and the paternally transmitted T-93/I-E8 haplotype combination cause pre-eclampsia and miscarriage in primagravidas." Therefore, it is at the heart of the present invention to screen for a plurality of genotypes in the fetus, its mother and its father. To restrict screening to only one of the polymorphisms from the application, as the Examiner wishes, would therefore obviate an important part of the essence and scope of the invention, and reduce its usefulness. The M.P.E.P. states:

> to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided to partially waive the requirements of 37 C.F.R. 1.141 and permit a reasonable number of such nucleotide sequences to be claimed in a single application. It has been determined that normally 10 such sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without

> restriction... Furthermore, nucleotides sequences encoding the same proteins are not considered to be independent and distinct inventions and will continue to be examined together. M.P.E.P. § 803.04.

Applicants respectfully submit that the above-quoted passage from the M.P.E.P. allows the Examiner to examine all of the polymorphisms in the instant application, and respectfully request that the Examiner withdraw the species election between the different polymorphisms.

Applicants submit that the methods of the invention encompass many methods (for example, multiplex sequencing or PCR reactions) that are capable of simultaneously testing multiple polymorphisms in a single test reaction. Indeed, it is routine for a person skilled in the art to carry out such procedures, and one of skill in the art would know from reading Applicants' specification that such procedures may be used in the methods of the invention. Accordingly, it would be unfair to limit the instant invention to a single polymorphism. Applicants further submit that even if the Examiner maintains that the products of the same gene are independent and distinct and wishes to examine them separately, the M.P.E.P. directs that a sufficient search and examination with respect to the different polymorphisms can be made without serious burden on the Examiner. As the M.P.E.P. states, "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." M.P.E.P. § 803.

The different polymorphisms are all variants of HLA-G. As such, the searches with regard to the variant gene products of the invention would be co-extensive and would not involve a serious burden on the Examiner.

However, in the event that the species restriction is maintained, Applicants hereby provisionally elect, with traverse, the HLA-G polymorphism of SEQ ID NO. 18. In the event that the Examiner agrees with Applicants' arguments regarding the traversal of this species election, Applicants hereby elect the CT polymorphism of codon 93 in Exon 3 and a deletion of

exon 8. Applicants are of the understanding that, upon allowance of a generic claim, Applicants will be entitled to claims directed to further species in addition to the elected species.

Finally, in addition to the above-described restriction requirements, the Examiner has further required a species election of the specific sequence primers to be used in the instant invention, where appropriate. Applicants respectfully submit a species election with respect to primers is both unfair and unnecessary. Applicants submit that a there is no need for primer sequences in a search of any of the methods of the invention, and that none of the instant claims recites primers or primer sequences. Indeed, Applicants are unaware of any previous instances where the sequences of primers were required for the search of method claims similar to those described in the instant application. Additionally, Applicants submit that a requirement to specify the sequences of primers unfairly limits Applicants' invention, because the methods may often achieve the same result using a variety of different primers. Accordingly, Applicants respectfully request withdrawal of the requirement to elect specific primers.

As the Examiner is aware, oligonucleotides must often be used in conjunction with other oligonucleotides in order to carry out their function or provide truly informative answers. In a purely illustrative embodiment, to test for C/T polymorphism in exon 93 with insertion of exon 8, Applicants select the primers described as SEQ ID NOs: 1 and 14, followed by 3, and to test for C/T polymorphism in exon 93 with deletion of exon 8, Applicants elect the primers described as SEQ ID NOs: 1 and 15, followed by 3. Accordingly, if the species election is maintained with respect to the primers, Applicants provisionally elect, with traverse, the primers of SEQ ID NOs: 1, 14, 15, and 3.

While Applicants disagree with the Restriction Requirement, it also is believed to be avoided by the newly amended claim set submitted herewith. Applicants submit that the claims, as amended herein, further define and clarify the subject matter of the invention, thus rendering the outstanding restriction moot. For purposes of initial search and examination, Applicants also

propose inclusion of those claims directed to the test kit recited in claims 66-71. Applicants submit that the search and examination of those claims will present significant overlap with the remainder of the claims.

In any event, should one or more aspects of the Restriction Requirement and/or species election be maintained, Applicants further respectfully request that rejoinder of some, if not all, of the remaining groups be considered by the Examiner following the search. Such rejoinder is amply supported by the foregoing arguments.

In view the foregoing, entry of the within amendments and reconsideration of the restriction are requested.

Early consideration and allowance of the application are earnestly solicited.

Respectfully submitted,

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